The Thalassemias in Clinical Practice

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• Thalassemia: definitions and pathophysiology
• Epidemiology
• Classification of thalassemia syndromes
• Diagnosis of thalassemia
• Treatment of thalassemia
**Hemoglobin**

- Hemoglobin is a tetramer of 2 pairs of unlike globin chains

<table>
<thead>
<tr>
<th>2 alpha chains</th>
<th>2 beta chains</th>
<th>$\alpha_2\beta_2$</th>
<th>Adult hemoglobin or HbA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 alpha chains</td>
<td>2 gamma chains</td>
<td>$\alpha_2\gamma_2$</td>
<td>Fetal hemoglobin or HbF</td>
</tr>
<tr>
<td>2 alpha chains</td>
<td>2 delta chains</td>
<td>$\alpha_2\delta_2$</td>
<td>Minor adult hemoglobin or HbA2</td>
</tr>
</tbody>
</table>

Alpha genes are encoded on chromosome 16
There are 2 copies of alpha genes on each Ch.16
Gamma, delta and beta genes are encoded on chromosome 11
There is a single copy of each of these genes on each Ch.11

![Diagram of Hb A: $\alpha_2\beta_2$ and Hb F: $\alpha_2\gamma_2$]
Thalassemias:
Quantitative defects of globin chain synthesis

**Thalassemia**
Inherited anemia
Inability to synthesize normal amounts of globin proteins

**α thal**: Decrease or absence of α-globin chains

**β thal**: Decrease or absence of β-globin chains

**Thalassemia Trait**
Heterozygote
Mild anemia that has insignificant effect on health

**α thal trait**

**β thal trait**

**Thalassemia Disease**
Heterozygote, Homozygote or Compound Heterozygote
 Moderate or severe anemia

May not require transfusion: Thalassemia intermedia

Requires regular transfusions: Thalassemia major
Molecular Pathogenesis: beta thalassemia

Normal

Beta-thalassemia Trait

Beta-thalassemia Major or Intermedia
Molecular Pathogenesis: alpha thalassemia

Globin Genes

Globin Chains

Red Blood Cell

**α** β

**α** β

**α** β

**α** β

Normal
M: 14.5-16.5; F: 13-15

A Thal Trait
M: 12-14; F: 10.5-12.5

Hb H Disease
M: 10-12; F: 8.5-10.5

Alpha Thal Major
Severe Anemia in Fetus
Transfusion Dependence in Thalassemia Syndromes

- No Transfusions
  - Thal Trait
  - Hb H Disease
  - Heterozygous β thal intermedia

- Occasional Transfusions
  - E Beta Thal
  - Hb H Constant Spring

- Regular Transfusions for Symptoms
  - E Beta Thal
  - Beta Thal Intermedia

- Regular Transfusions for Survival
  - E Beta Thal
  - Beta Thal Major
  - Alpha Thal Major
Annual Births of Severe Thalassemia Syndromes

Modell 2008, Bull WHO
Distribution of Thalassemia in China

Adapted from Zeng & Huang. J Med Genet. 1987:578 and others
Distribution of Thalassemia in USA (estimated)

Oakland Data, HRSA, TCRN, plus extrapolation
Prevalence of Hemoglobinopathies in California

Birth Prevalance of Hemoglobinopathies in California
per 100,000 births, July 2005 - July 2010, n= 2,282,138

- SICKLE CELL DISEASE
- THALASSEMIA SYNDROMES

CA Newborn Screening Program
Distribution of Ethnicities at Oakland

- Chinese: 18%
- Laotian: 12%
- Vietnamese: 8%
- Filipino: 6%
- Asian, other: 6%
- Med: 3%
- Caucasian: 2%
- Italian: 5%
- Mid East: 7%
- Other: 2%
- Afghani: 4%
- Pakistani: 5%
- Indian: 8%
- Unk: 1%
- AA: 2%
- Thai: 5%
- Cambodian: 5%
Diagnosis of Thalassemia: Thalassemia Trait

- **First Step**: suspect thalassemia trait on CBC
  - Mild anemia: Hemoglobin 10-12 g/dL
  - Microcytosis: MCV <80
  - Hypochromia: MCH <28
  - RBC count Normal or ↑
  - RDW Normal

- **Next Step**: Hemoglobin Electrophoresis
  - Beta thalassemia trait: elevated A2 (>3.5%)
  - Alpha thalassemia trait: normal hemoglobin pattern

- **Final Step**: DNA testing for mutations or deletions

- **What is the best time to screen at risk population**
  - Beta thal trait: at 1 year CBC
  - Alpha thal trait: At birth (currently not done), or at 1 year CBC
  - Also screen first degree relatives with CBC

- **Genetic counseling should follow screening**
  - Prepare PCP’s caring for at risk population to provide counseling
  - Counseling is different for alpha and beta thalassemia

<table>
<thead>
<tr>
<th></th>
<th>Thal Trait</th>
<th>Iron Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild anemia: Hemoglobin</td>
<td>10-12 g/dL</td>
<td>10-12 g/dL</td>
</tr>
<tr>
<td>Microcytosis: MCV</td>
<td>&lt;80</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Hypochromia: MCH</td>
<td>&lt;28</td>
<td>&lt;28</td>
</tr>
<tr>
<td>RBC count</td>
<td>Normal or ↑</td>
<td>Low</td>
</tr>
<tr>
<td>RDW</td>
<td>Normal</td>
<td>High</td>
</tr>
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</table>
Diagnosis of Thalassemia Disease

• Prenatal diagnosis
  • When both parents are known carriers of thalassemia mutation
  • Test second parent if one parent is known thalassemia trait
  • Prenatal testing (CVS or amnio) if both have beta trait or alpha trait
  • No consequence if one parent has alpha and one has beta trait

• Newborn screening for thalassemia syndromes
  • Alpha thalassemia: Hb Bart’s
  • Beta Thalassemia: HbF
  • E beta Thalassemia: HbE

• Diagnosis in childhood
  • Hemoglobin <10 g/dL, exclude iron deficiency
  • Microcytosis (sometimes mild), hypochromia, target cells, nucleated RBC
  • Splenomegaly, elevated bilirubin, growth impairment
  • Hemoglobin electrophoresis: High HbF, or presence of HbE or HbH
  • Confirm by DNA testing
### Common Thalassemia Syndromes

- **Beta thalassemias:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotype</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta thal major</td>
<td>2 beta mutations</td>
<td>Hb &lt;7 g/dL</td>
</tr>
<tr>
<td>Beta thal intermedia</td>
<td>2 beta mutations</td>
<td>Hb &gt;7 g/dL</td>
</tr>
<tr>
<td>E beta thal</td>
<td>1 beta mutation with E mutation</td>
<td>Hb 4-9 g/dL</td>
</tr>
</tbody>
</table>

- **Alpha thalassemias:**

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<tr>
<th>Condition</th>
<th>Genotype</th>
<th>Hemoglobin</th>
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</thead>
<tbody>
<tr>
<td>HbH disease</td>
<td>3 alpha gene deletion</td>
<td>Hb 8-12 g/dL</td>
</tr>
<tr>
<td>HbH Constant Spring</td>
<td>2 alpha gene deletion + Constant Spring mutation</td>
<td>Hb 7-10 g/dL</td>
</tr>
<tr>
<td>Alpha thal major</td>
<td>4 alpha gene deletion</td>
<td>Fetal hydrops</td>
</tr>
</tbody>
</table>
Treatment of Thalassemia

• Deciding between regular transfusions and conservative management
• Pros and cons of transfusions
• Alternatives to transfusions
• Curative therapies
Transfusion Dependence in Thalassemia Syndromes

- **No Transfusions**
- **Occasional Transfusions**
- **Regular Transfusions for Symptoms**
- **Regular Transfusions for Survival**

- **Alpha-Beta imbalance**
- **Hemoglobin at baseline**
- **Fetal hemoglobin compensation**
- **Oxygen delivery efficiency**
## Comparison of Average Hemoglobin Levels

<table>
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<tr>
<th>Category</th>
<th>Hemoglobin Level</th>
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</thead>
<tbody>
<tr>
<td>Individuals without thalassemia</td>
<td>13-16 g/dL</td>
</tr>
<tr>
<td>Thalassemia intermedia not receiving transfusions</td>
<td>6-9 g/dL</td>
</tr>
<tr>
<td>Thalassemia major receiving regular transfusions</td>
<td>11-12 g/dL</td>
</tr>
</tbody>
</table>

### Why not transfuse all individuals with thalassemia intermedia?

...
# Complications of Low Hemoglobin in Non-Transfused Thalassemia

## Children
- Bone changes: face and head size
- Feeding difficulties
- Sweating
- Lack of weight gain
- Growth delay
- Splenomegaly

## 10-15 years
- Growth delay
- Pubertal delay
- Progressive splenomegaly
- Facial bone changes
- Fatigue
- Extramedullary masses

## Adults
- Extra-medullary masses
- Fatigue
- Pain
- Thrombosis
- Pulmonary hypertension,
- Cerebral vaculopathy
- Leg ulceration
- Fractures
Transfusions have become very safe, but still have risks

Risks
- Iron overload
- Antibody formation
- Viral infections
- More hospital visits

Benefits
- Activity, appetite, growth
- Prevent bone changes
- Prevent spleen enlargement
Deciding on chronic transfusions

• Beta/Beta thalassemia
  • Baseline hemoglobin <7 g/dL, with or without symptoms
    Or
  • Baseline hemoglobin >7 g/dL AND symptoms of anemia

• E Beta Thalassemia
  • Symptoms of anemia

• Hemoglobin H Disease
  • Intermittent transfusions in Hb H Constant Spring
  • Transfusions are not needed in deletional Hb H disease
Beta Thalassemia Major: Natural History

- **Transfused Symptomatic:** 10-20 years
- **Pre-symptomatic:** 0-10 years

**Complications:**
- Growth Delay
- Hypogonadism
- Diabetes
- Hypothyroidism
- Death
- Arrhythmias
- Cardiac Failure
- Liver Fibrosis
- Osteoporosis
- Diabetes
- Hypothyroidism
- Hypogonadism
- Growth Delay

**Hemoglobin:** 9.5-10.5 g/dL
**Systemic Iron**
Control of systemic iron burden is central to long-term prognosis

Control with normal iron

Patient with iron overload

- Methods to measure iron
  - Serum ferritin
  - Liver biopsy

- Non-invasive
  - Liver MRI
  - Biosusceptometry (SQUID)
  - Cardiac iron with MRI T2*
  - Pituitary and Pancreatic MRI

Iron staining (Prussian Blue)

Courtesy of M Weyhmiller, PhD, P Harmatz, MD
Beta Thalassemia Major: Natural History
Transfused & Chelated

<table>
<thead>
<tr>
<th>Normal Growth</th>
<th>Normal Puberty</th>
<th>Marriage and Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Skeletal Changes</td>
<td>Education</td>
<td>Productive Adult Life</td>
</tr>
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Pre-transfusion Hemoglobin 9.5-10.5 g/dL

- Multi-Specialty Care
- Nutrition
- Endocrinology
- Hepatology
- Cardiology
- Reproductive Specialist
- Psychosocial Support

Periodic Comprehensive Evaluation

Regular Chelation

Liver Iron Concentration 3-6 mg/g

Birth
Options for Non-Transfused Thalassemia

• Hydroxyurea
  • Effective in a subgroup of patients with beta thalassemia intermedia

• Splenectomy: no longer used as elective treatment

• Luspatercept (investigational)
  • Improves survival of red blood cell that are forming in the bone marrow
  • Initial clinical trial in transfusion-dependent thalassemia
  • Future trial in non-transfused thalassemia

• Hepcidin or hepcidin-mimics (investigational)
  • Expected to improve alpha:beta imbalance
  • No current clinical trials in non-transfused thalassemia
Cure for thalassemia

• Bone marrow transplant
  • Sibling Donor: >90% chance of success
  • Unrelated donors: Complication rates high

• Gene therapy
  • Lentiviral vectors
  • Gene Editing

Lentiviral gene therapy in transfusion-dependent E-beta thal
Thalassemias in Clinical Practice: Thalassemia Trait

Identify and investigate microcytic anemias

- Use ethnicity information to increase pre-test probability
- Use Hgb electrophoresis and DNA testing to confirm if suspicion is strong or response to iron supplementation incomplete
- Special attention to microcytic anemia during antenatal testing

Incorporate essentials of genetic counseling in primary practice

- Understand the reproductive implications of alpha versus beta thalassemia traits
- Advocate for alpha thal trait screening in newborn period
Thalassemias in Clinical Practice: Thalassemia Disease

Manage milder thalassemia syndromes in community setting with support from thalassemia center

- Identify HbH disease and others that do not need transfusions
- Awareness of long term complications: iron overload, bone disease, others
- Awareness of the effect of thalassemia on quality of life

Severe Thal syndromes need specialty care at Thal center

- Beta thal intermedia or major, most E beta-thalassemia
- Identify and refer pregnancies at risk for alpha thalassemia major early
- Support the thal centers by provide life-long primary care to the patients
Core Staff and Collaborators

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Center Director

Ashutosh Lal, MD
Director of Clinical Program

Lynne Neumayr, MD
Administrative Director

Sylvia Titi Singer, MD
Research Hematologist

Shannon Gaine, FNP
Nurse Practitioner

Wendy Murphy, MSW
Social Work

Raquel Manzo
Clinic Coordinator

Shanda Robertson
Database Manager

Mark Walters, MD, Stem Cell Transplant
Carolyn Hoppe, MD, Red Cell Reference Lab
Ellen Fung, PhD, Nutrition & Bone Health
Marcela Weyhmiller, PhD, Iron Measurement
Roland Fischer, PhD, Iron Measurement
Paul Harmatz, MD, Hepatology
Eric Padua, MD, Radiology
Greg Kurio, MD, Cardiology
Shannon Kelly, MD, Blood Centers of Pacific
Tariq Ahmad, MD, Endocrinology
Frans Kuypers, PhD, Red cell laboratory
Marsha Treadwell, PhD, Clinical Psychology
Patrick Walter, PhD, Iron Metabolism
Cassandra Calloway, PhD, Molecular genetics
Jennifer Ferguson, PNP, Clinical Research

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